DETAILED ACTION

Claims 1 and 22-28 are pending.

Claims 22, 23, 25, 26, and 28 are withdrawn from examination as detailed below.

Claims 1, 24 and 27 are examined on the merits.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 11/16/2009 and 12/01/209.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Election/Restrictions

1. In the reply filed on 02/26/2009 Applicants elected for examination of the claims as they require Haplotype No.5 from Table 8, and subsequently received an Office Action wherein the methods requiring the particular analysis of Haplotype No.5 from Table 8 were examined. The instantly presented claims require "a gene polymorphism", as recited in claim 1, selected from a listing polymorphisms identified by position within a gene and SEQ ID NOs. In the instant case the particular polymorphism IVS3+A6151G of SEQ ID NO: 28 is one polymorphic position of the originally elected Haplotype. The Requirement for Restriction between the particular combination of the positions of the elected haplotype and the subcombination of the particular position IVS3+A6151G of SEQ ID NO: 28 (as recited in claim 1) is withdrawn. This withdrawal

does not effect the restriction requirement as in still applies to other subcombinations of the originally elected haplotype, nor any other positions disclosed in the specification of the instant application. The methods of the instantly presented claims are examined in so far as they require the analysis of the single particular position IVS3+A6151G of SEQ ID NO: 28.

Claims 22, 23, 25 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (i.e.: methods requiring the analysis of non-elected polymorphic positions), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 02/26/2009.

The Ikeda Declarations

2. The declarations of Ikeda under 37 CFR 1.132 filed 11/16/2009 and 12/01/2009 are insufficient to overcome the rejection of claims based upon 35 USC 112 1st paragraph for lack of enablement. The deficiencies of the declarations are addressed later in this Office Action in the Response to Remarks following the maintained rejection.

Objection to the Amendments to the Specification

3. The amendment filed 11/16/2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

Applicants have amended Table 4, and the sequence listing of the instant application, to include newly presented SEQ ID NO: 100. Applicants have argued (p.11 of the Remarks of 11/16/09 and part 15 of the Declaration of 11/16/2009) that there is basis in the specification as originally filed for the newly presented sequence where the specification contemplates the use of probes and discloses other probes that are 101 bases long with a polymorphic position at position 51. However, as there is no disclosure of the required bas sequence to design the newly presented probe, nor is there basis for such a probe in any proper incorporation by reference, the newly set forth probe is new matter.

Applicants have amended Table 6 to change the values of linkage disequilibrium for the IVS3 +6151 and +8449 positions. Applicants have argued (parts 16 and 17 of the Declaration of 11/16/2009) that there is basis in the specification as originally filed where the skilled artisan practicing the method to analyze linkage disequilibrium would have determined that the values provided by Applicants in there own specification as originally filed were incorrect. Applicants have not pointed to any portions of the specification to provide a basis for the particular amended numbers. There is nothing in the specification as originally filed that would indicate that analysis of some data provided in the specification as originally filed would lead to the conclusion that the amended numbers would be garnered from any analysis of the data. As such the amendments to Table 6 are new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Withdrawn Claim Objections

4. The objection to as set forth on pages 2-3 of the Office Action of 05/15/2009 are **WITHDRAWN**. With regard to the specific recitation of non-elected subject matter in the alternative as present in the instant claims it is noted that no claim is allowed in this Office Action. Prior to the allowance of any claim, non-elected subject matter that is not rejoined with the elected combination and also allowed will be required to be deleted from the claims.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

5. The rejections of claims under 35 USC 112 2nd ¶ as being indefinite, as set forth on pages 3-4 are **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

6. Claims 1, 24, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejected claims are unclear over recitation of the phrase “IVS3 + A6151G of SEQ ID NO: 28”, where the polymorphism as disclosed in the specification is at position 51 of SEQ ID NO: 28, and thus the nomenclature of IVS3+ and 6151 are not relevant to the recite SEQ ID NO. The claims may be made more clear if the unclear phrase is amended to recite "IVS3 +A6151G of the human mu opiod receptor gene,

wherein IVS3 +A6151G is either an A or a G at the position in the mu opiod receptor gene corresponding to position 51 of SEQ ID NO: 28".

The rejected claims are unclear over recitation of the limitation "wherein said gene polymorphisms are in linkage disequilibrium with IVS3 + A6151G of SEQ ID NO: 28. As detailed earlier in this Office Action, the instant claims are examined as they require the detection of the particular position IVS3 + A6151G of SEQ ID NO: 28, and as such it is unclear how the elected position is considered to be in linkage disequilibrium with itself.

Withdrawn Claim Rejections - 35 USC § 112 1st¶ - Written Description

The rejection of claims under 35 USC 112 1st ¶ for lack of adequate written description, as set forth on pages 4-6 of the Office Action of 05/15/209, is **WITHDRAWN** in light of the amendments to the claims.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement

7. Claims 1, 24 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The instant claims are drawn to methods of evaluating sensitivity of a human subject to a drug (as recited in claim 1) and requires linking the gene polymorphism IVS3+A6151G of SEQ ID NO: 28 to drug sensitivity.

The claims require knowledge of a correlative association between a polymorphism and a wide variety of phenotypic qualities related to any sensitivity to a variety of drugs as recited in claim 1.

Direction provided by the specification and working example

The instant specification provides an example (e.g.: p.13) of the identification of polymorphisms in the human mu opioid receptor (Tables 1, 2, and 4), and several haplotypes of some particular polymorphisms (e.g.: Table 5). The instant specification provides an analysis of linkage disequilibrium of mu opioid receptor polymorphisms (Table 6).

The specification asserts (e.g. p.12-13) that analyzing haplotypes makes it possible for one to elucidate drug sensitivity, and thus allows one to know in advance an appropriate amount of drug to be administered to an individual before administering the drug. The only analysis of any association of between the elected haplotype (i.e. haplotype No. 5 of Table 8) and a phenotype is an analysis of haplotype frequency in patients addicted to methamphetamines as compared to haplotype distribution in non-addicted subjects (p.52 – Example 4).

The specification provides an analysis (Table 10) of the single polymorphism IVS3 +A6151G in case and control subjects in methamphetamine addicted populations. Table 10 provides data pertaining to two populations, wherein in one population it

appear the A allele is overrepresented in methamphetamine addicted cases (i.e. group 1), however in a second population (i.e. group 2) there is no association between genotype and addiction (i.e. p=0.9060).

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to the detection of any particular haplotype or genotype in a known gene is high, the unpredictability with regard to the association of any particular haplotype or genotype with a particular phenotype is even higher. The unpredictability is demonstrated by the prior art and the post-filing art, and the instant specification.

Because the claims encompass diagnostic methods requiring positions that are in linkage disequilibrium to other positions, it is relevant to point out that the instant specification teaches the unpredictability in extrapolating phenotypic associations (as required by the claims) among different polymorphic content asserted to be in linkage disequilibrium. For example, while Table 6 asserts a significant (D' > 0.7) linkage disequilibrium between IVS2 +691 and A118G, this assertion is not supported by the data in Table 7 which asserts an association between IVS2 +691 and methamphetamine addiction but no significant association between A118G and the same phenotype.

The specification further demonstrates the unpredictability of associating the required nucleotide content (i.e. IVS3+A6151G) with the required drug sensitivity phenotypes. Table 10 of the instant specification shows that while in one study population there is a trend toward the A allele being overrepresented in addicted

subject, no such association is seen in a separate population. This unpredictability is also shown in Ide et al (2006) (as cited on the IDS of 08/17/2009), where there is no significant association between the IVS3+6151 position and methamphetamine addiction in a study population (Tables 3 and 5 of Ide et al). As evidence of the unpredictability of gene association studies, Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Additionally, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

With particular regard to associations with polymorphisms in the mu opioid receptor, the prior art and post-filing art indicate the unpredictability in establishing

robust and reliable associations that are consistently accurate in diagnoses. For example, Coller et al teaches a meta analysis of the A118G SNP, where a thorough analysis indicates a lack of association between the polymorphism and opioid dependence, even where such an association was previously asserted in several populations. Similarly, while the instant specification asserts an association between IVS2 +691 and methamphetamine addiction (Table 7), and the claims generically encompass and specifically recite ethanol (e.g. claim 3) as a drug for the claimed methods, Bergen et al teaches that there is no significant association between IVS2 +691 and alcohol dependence.

Finally, with regard to the haplotypes comprising the IVS3+ A6151G position (and in fact all the haplotypes of Table 8 and the analysis of methamphetamine addiction) it is relevant to point out that the specification (p.56-57) teaches that none of the associations were statistically significant, with a p-value of p=0.40. Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include large case:control studies in multiple populations of any subject organism of interest to

demonstrate a reliable association of any different haplotype, as estimated by different polymorphisms, with sensitivity to any drug. One would have to perform large case:control studies to establish whether or any associations are reliable and robust. Such experimentation would be extensive, especially considering in the lack of data presented in the instant specification regarding haplotypes and drug sensitivity. Even if one were to carry out such experimentation, there is no assurance that a reliable and consistent association of haplotypes and drug sensitivity would be identified.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments and Declarations of 11/16/2009 and 12/01/2010 have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Initially it is noted that in light of the amendments to the claims the portions of the rejection as set froth in the Office Action of 05/15/2009 regarding the claims as they encompass the analysis of non-human subjects has been withdrawn from the instant rejection.

Applicants have argued (p.17 of Remarks of 11/16/2009) that Table 10 of the instant specification describes that IVS3+A6151G is associated with methamphetamine sensitivity, and that the skilled artisan would recognize that other positions (e.g. IVS3+8449) are in strong linkage disequilibrium with the IVS3+ 6151 position. The argument is not persuasive. As set forth in the instant rejection, to assert that the specification describes an association with methamphetamine sensitivity is to ignore the data of the specification pertaining to 'group 2' as presented in Table 10. At best, considering all of the data available in the specification, the data demonstrates that any asserted association is unpredictable, and not reliable in application to different subjects in different populations. Furthermore, as set forth earlier in this Office Action, the specification as originally filed (i.e.: Table 6) does not support a consistent measure of strong linkage disequilibrium between the required IVS3+ 6151 position and the IVS3+ 8449 position discussed in the Remarks as taught by Fukuda et al (in press). As such, the attempt to provide evidence of enablement of the required IVS3+ 6151 position with post-filing data of the IVS3+ 8449 position is not persuasive.

The Declarations of 11/16/2009 and 12/01/2009 are not persuasive to withdrawn the rejection for the reasons as detailed above regarding the Remarks. The Declarations (i.e. the Declaration of 11/16/2009 (part 7) and the Declaration of 12/01/2009 (part5)) assert that Table 10 of the specification teaches the association of the IVS3+6151 position with methamphetamine addiction. However, as detailed above, the assertion dose not account for the data pertaining to 'group 2', where the asserted association is absent. Parts 8-11 of the Declaration of 11/16/2009, and parts 5-6 of the

Declaration of 12/01/2009, attempt to provide evidence of the enablement of the instant methods, which require the IVS 3+6151 position, based on linkage with the IVS3+8449 position, which has been discussed earlier in this Response to Remarks. Finally, the Declaration of 12/01/2009 presents evidence (i.e. part 7 of the Declaration) that "confirms that IVS3+A6151G is not only associated with methamphetamine use, but is also associated with 24 hour postoperative fentanyl use". However, the data of the Declaration of 12/01/2009 does not present any evidence regarding methamphetamine use. Furthermore, the data provided in the declaration of 12/01/2009 is specific to 24 hour postoperative fentanyl use, where such a requirement does not appear in the specification as originally filed (i.e. a claim requiring such a limitation would be new matter), and considering the unpredictability of the subject matter the data regarding 24 hour postoperative fentanyl use would not be reliably extrapolated to other drugs (as recited in instant claim 1).

Conclusion

8. No claim is allowed.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
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